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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,118	09/14/2004	Henrik Semb	034005-008	7902

21839 7590 11/10/2009

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POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
11/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/500,118	SEMB ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9-20,22-56,60-62,64 and 65* is/are pending in the application.

4a) Of the above claim(s) *22-34 and 36-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 9-20, 35, 60-62, 64, 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/23/09 has been entered.

Applicants have not filed remarks or amendment with the RCE submission. The Examiner responds to Applicants' remarks, filed after-final, 9/24/09. Claims 1-5, 9-20, 22-56, 60-62, 64, 65 are pending; claims 1-4, 11, are amended; claims 22-34, 36-56 are withdrawn; claims 1-5, 9-20, 35, 60-62, 64, 65 are under current examination.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-21, 35, 57-61) in the reply filed on 1/12/07 is acknowledged.

Claims 22-34, 36-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/12/07.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5, 12, 13, 16-20, 62, 64, 65 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (2001) when taken with Thomson (1998) as evidenced by Stem Information (National Institutes of Health), when taken with Rijnders *et al.* and in further view of Lanzendorf *et al.* when taken with US Pat. No. 6,875,607 (published April 5, 2005; filed November 9, 1999.

Applicants' Arguments. The claims have been amended to recite that the step of isolating the ICM cells by mechanical dissection into pieces does not comprise the use of immunosurgery. Applicants argue that one of ordinary skill in the art would not have reasonably predicted that the ICM cells could be successfully isolated by mechanical dissection into pieces without the use of immunosurgery. Particularly, Applicants argue that the methods applied for isolating ICM cells prior to the time of the claimed invention relate to using immunosurgery. Thus,

Applicants argue that given the specificity and uniformity of the art published before the time of filing included immunosurgery, nothing in the art would teach or suggest how to isolate the ICM without the use of immunosurgery. See pages 13-14 of the Response.

Applicants argue that the passage that the Examiner refers to, with respect to mechanical dissociation, is with regard to passaging the cells, but not isolation of the inner cell mass cells. Applicants argue that in addition to the fact that none of the skilled artisans at the time of filing arrived at the claimed invention, the heterogeneous structure of the blastocyst compared to the homogenous nature of the isolated and cultured ICM make it non-obvious to apply a method for passaging to isolating the ICM. The isolated and propagating ICM forms a relatively uniform colony, whereas the blastocyst is a heterogeneous structure comprising the ICM surrounded by the zona pellucida and trophectoderm. Applicants argue that in reviewing the literature after the time of filing, it seems that the method claimed in the instant invention with documented advantages, for example, that in using mechanical dissection, the direct yield was more than twice as high as the yield from immunosurgically isolated cultures. Additionally, Applicants point to Strom who teach that mechanical isolation of the ICM yielded higher numbers of viable cell lines. See pages 14-15 of the Response.

Response to Arguments. These arguments have been fully considered, but are not persuasive. In particular, Applicants are arguing limitations that are not within the scope of the claim. Applicants' arguments regarding isolating the ICM from a blastocyst is not a limitation of the claims. For example, claim 1, step ii); claim 2, step ii); claim 3, step ii); claim 4, step ii) recites culturing the blastocyst with fibroblast feeder cells to establish colonies of ICM cells. Therefore, the claims relate to cultured colonies of ICM cells, and not direct isolation of the ICM cells from a blastocyst, as suggested and argued by Applicants. The working examples of the specification teach the establishment of undifferentiated stem cells by allowing

blastocysts to be cultured on fibroblast feeder cells (Examples 1-2) and then the expansion of the colonies by manual dissection (see Example 4). The specification does not teach the mechanical dissection of the intact blastocyst, as suggested by applicants. Each of the working examples teaches that the blastocyst is hatched and allowed to form colonies on feeder cells. Therefore, Applicants' working examples are also directed to the manual passaging of colonies. See also, page 17, lines 1-2; Example 4, p. 17, lines 33-34. The cited art of record clearly teaches how to recognize a colony of cultured undifferentiated cells. Particularly, the '607 reference teaches the mechanical cutting of colonies in order to passage ES cells. Thus, given that the claims are directed to isolating colonies of ICM cells, one of skill in the art would reasonably recognize that the techniques of isolating cell colonies would be similar and applicable. That is, one of skill in the art would be knowledgeable in art-recognized methods to isolated inner cell mass cells, including using mechanical dissection, or immuno-surgery and that these techniques were well within the skills of the ordinary artisan. Thus, it would be obvious to the skilled artisan to substitute any method for isolation of ICM cells for another, to achieve the predictable result of isolation of ICM cells. Accordingly, the prior rejection of record is maintained.

With regard to Applicants' arguments regarding the post-filing art regarding an increased yield of viable cell lines, it appears that Applicants are attempting to argue an unexpected result. See MPEP §716.02(d) which states, "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." The claims do not reflect the unexpected result that Applicants are asserting, thus, the cited combination of art is sufficient to arrive at the claimed invention. However, Applicants are cautioned that amendment(s) to the claims do not contain new matter.

Rejection

Thomson (2001) teach methods for the production of primate embryonic stem cells, including human ES cells. In particular, they teach the isolation of a blastocyst, isolating cells from the inner cell mass (ICM) of the blastocyst, and plating the ICM cells on embryonic feeder layers (see col. 4, lines 38-49). They teach that these methods can be used in deriving human ES cell lines (col. 7, lines 4-10). In particular, they teach isolating blastocysts from a primate, removing the zona pellucida using pronase, and then removal of the intact inner cell mass cells by gentle pipetting and plated on inactivated, irradiated embryonic fibroblasts (col. 8, lines 32-40). They teach that the dissociated cells are then replated on embryonic feeder layers, and cells demonstrating ES-like morphology are then individually selected and propagated. See col. 8, lines 50-59. They teach the co-culture of human blastocysts with human oviductal cells to produce expanded human blastocysts (see col. 9, lines 23-32). Thomson teach that their human ES cell line is stable (see issued claim 1). They further teach using mouse feeder cells, and particular, mouse STO cells (ATCC 56-X), which are irradiated mouse fibroblast feeder cells.

Thomson (1998) provide specific guidance to show that the production of human ES cells requires human embryos, which are produced by IVF (see p. 1147, col. 2, #6). With regard to claim 20, although Thomson (1998) teach that their cells have been passaged for more than 8 months, they do not specifically teach that the cells have a proliferation capacity, in an undifferentiated state, for more than 21 months, as required by part i) of claim 20. However, The NIH stem cell information provides evidence that the exact cell line described in the Thomson (1998) paper, the H9 cell line, has the proliferation capacity for more than 21 months, stating that, "[T]he H9 cell line has divided for nearly two years *in vitro*." See page 2, first sentence. Thus, this citation describes an inherent property of the cells, and shows

that they have a proliferation capacity of over 21 months. Furthermore, Thomson (1998) provide the various characteristics required by the claim 20, namely that the ES cell lines exhibited a normal karyotype (see page 1145, 2nd col.) (see part (ii) of the claim 20); had the developmental potential to form the derivatives of all three germ layers, both *in vitro* and *in vivo* (see Abstract, and page 1146, 1st col., 2nd full ¶) (part iii of the claim); exhibited appropriate markers, including expression of SSEA-3, SSEA-5, TRA-1-60, TRA-1-81 (p. 1145, 3rd col., last ¶), as required by part (iv) of the claim; did not express SSEA-1 (p. 1146, 1st col., 1st ¶); formed teratomas when injected into immunocompromised mice and is capable of differentiation (p. 1146, 2nd full ¶), as required by steps vi-vii of the claim.

Neither Thomson (2001), nor Thomson (1998) teach using a fertilized oocyte having a grade 1 or 2 to obtain a blastocyst of grade A or B, as recited in step (i) of claims 1-3. The instant specification defines Grade 1 fertilized oocytes as those which have even blastomeres, with no fragments, and Grade 2 fertilized oocytes as those with <20% fragments (see page 4, lines 1-52); Grade A blastocysts are those with expanded distinct inner cell mass cells 5-7 days after fertilization, and Grade B blastocysts are not expanded but, otherwise like Grade A (p. 4, lines 10-11). Rijnders *et al.* provide specific guidance with regard to the identification of class I and class II embryos, which are defined similarly as the instant specification's definition (see p. 2870, 1st col., Embryo Pre-selection and Selection) and teach that class I and II embryos produced a higher percentage of blastocysts, and had less embryos that arrested in development of degenerated (see Abstract). Lazendorf *et al.* teach methods of identification of Grade 1 and 2 (analogous to the specification's definition of Grade A and B) blastocysts and they teach the hatching of the blastocysts (see page 134, 1st col.). They teach that some of the embryos, which were grade 1, hatched spontaneously, and that one blastocyst was grade 2, and required mechanical removal of the zona pellucida (see p. 135, 1st col, Results, 1st ¶).

They teach isolating inner cell masses from the blastocysts and producing embryonic stem cell lines.

Neither Thomson (2001), Thomson (1998), Rijnders or Lazendorf specifically teach propagating human blastocyst-derived stem cell colonies by repeatedly passaging the cells every 4-5 days wherein each passaging step comprises manually dissecting the inner homogenous structure of the human blastocyst-derived stem cell colonies to form pieces of the same and placing the pieces on inactivated fibroblast feeder cells. However, prior to the time of filing of the instant invention, the '607 patent teaches the production of undifferentiated human ES cells, and particularly teaches methods of propagating ES cells every 5-7 days of about 100 cells using mechanical dissociation. In particular, they teach that Ca/Mg free PBS medium was used to reduce cell attachments, and that when cell dissociation is partial, mechanical dissection using a sharp edge of a pipette is used with cutting and isolation of the clumps. They further teach that in an alternative approach, the combined approach of mechanical cutting of the colonies is performed to cut the colonies into about 100 cells, and the sharp pipette was also used to remove differentiated areas of the colonies. The clumps were then detached and picked up by micro-pipette and transferred to a fresh feeder layer. See col. 18, lines 1-27. Additionally, the '607 patent teaches that the fibroblast feeder cells can be of human or mouse origin (col. 9, lines 60-67). Accordingly, the '607 patent provides guidance for the newly added embodiments. In particular, they teach passaging the cells every 5-7 days, using a sharp pipette (manual dissection). Because the '607 patent teaches cutting non-differentiated cells and removing differentiated cells, this implicitly refers to the "inner homogenous structure" of the cell colonies (*i.e.*, the portion of the colony which would contain undifferentiated ES cells). Although the '607 patent does not explicitly teach cutting the ICM cells into pieces, one of skill would be readily apprised of variously known techniques, such as cell

dissociation taught by the '607 patent for propagating cells, for use in isolating the ICM cells.

Accordingly, it would have been obvious for one of ordinary skill in the art, to combine the teachings of Thomson (2001), Thomson (1998), who teach the production of human ES cell lines from human blastocysts, and with the teachings of Rijnders and Lazendorf, and using the methods taught by the '607 patent to propagate the ES cells using mechanical dissection, with a reasonable expectation of success. One of ordinary skill would have been motivated to use the method of identifying fertilized oocytes/embryos of Grade 1 or 2, as taught by Rinjnders to increase the number of embryos that are capable of producing blastocysts. One of skill ordinary skill in the art would have been also motivated to use the methods, taught by Lazendorf *et al.* to identify blastocysts of Grade A or B, in order identify cells which have clearly defined inner cell masses, which would increase the probability of producing a successful ES cell line. One of ordinary skill in the art would have been motivated to use the methods taught by the '607 patent to propagate hES cells because one of skill in the art would be readily apprised of various methods in which to propagate hES cells, including chemical or mechanical means. See also, '607 patent, col. 4, lines 10-18.

The combined teachings of Thomson (2001), Thomson (1998), Rinjnders, Lazendorf and the '607 patent teach the claimed invention because the teach the general methods of selecting particular human fertilized oocytes or blastocysts for the production of human ES cell lines (claims 1-3), they teach that the blastocyst can be spontaneously hatched (claim 5); they teach methods to propagate the cells by mechanical dissection (claims 1-3); wherein the zona pellucida of the blastocyst has been partially digested (claim 12); with a digestive agent (claim 13); wherein the feeder cells are embryonic feeder cells (claim 16); wherein the feeder cells in steps ii) and iv) are the same or different, and originate from an animal source (claim 17), particularly mouse (claim 18); wherein the feeder cells are mitotically

inactivated (claim 19); the characteristics required by the stem cell line (claim 20); wherein the fibroblast feeder cells are either mouse or human embryonic fibroblast feeder cells (claim 62); wherein the feeder cells are human (claim 64) or mouse fibroblasts (claim 65).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 4, 9, 10, 60 and 61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (2001) when taken with Thomson (1998) when taken with Rijnders *et al.,* Lanzendorf *et al.* in further view of and US Pat. No. 6,875,607 (published April 5, 2005; filed November 9, 1999)as applied to claims 1-3, 5, 6, 12, 13, 16-20, 62, 64, 65 above, and further in view of Marshall *et al.* (Methods in Molecular Biology: *Isolation and Maintenance of Primate Embryonic Stem Cells* 158: 11-18, January 2001). This is new ground of rejection.

Applicants have provided no substantive arguments for this rejection. The Examiner has addressed Applicants' arguments above.

Rejection

Thomson (2001), Thomson (1998), Rijnders, Lazendorf and the '607 patent have been described above. They do not teach the specific densities of the feeder cells required by the claims. However, Marshall discuss the isolation and maintenance of primate embryonic stem cells. They specific teach that the mouse embryonic fibroblasts, which are used as feeder cells, should be plated at 50,000 cells/cm^2 (see page 13, Section 3.1, #3). Thus, Marshall teach cell densities that are less than 60,000 (claims 4 and 9); "about" 45,000 cells/cm^2 (claim 10); less than 55,000 cells/cm^2 (claim 60) and "less than 50,000 cells/cm^2 (claim 61). Furthermore, Marshall teach that the cells should be passaged four to six days after immunosurgery (see p. 13, 3.2, #9), and thus, fulfill the limitation of claim 8.

Accordingly, given the combined teachings of Thomson (2001), Thomson (1998); Rijnders, Lazendorf, the '607 patent, and Marshall, it would have been obvious for one of skill in the art to utilize the methods to produce blastocyst-derived stem cell lines, and passage the cells every 4-5 days, at a density of 50,000 cells/cm^2, as taught by Marshall, with a reasonable expectation of success. One of skill in the art would have been sufficiently motivated to utilize this amount of cells, as Marshall provide a specific protocol to maintain primate ES cells, and they state that because primate ES cells require "regular and meticulous attention to detail in all aspects of the culture process", one of skill in the art would turn to their protocol for direction and specific guidance with regard to the culture of primate ES cells. See page 12, 1st ¶.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (2001) when taken with Thomson (1998) when taken with Rijnders *et al.*, Lanzendorf *et al.* and in further view of US Pat. No. 6,875,607 (published April 5, 2005; filed November 9, 1999), as applied to claims 1-3, 5, 6, 12, 13, 16-20, 62, 64, 65 above, and further in view of Conner.

Applicants provide no substantive arguments with respect to this rejection. The Examiner has addressed Applicants' arguments above.

Thomson (2001), Thomson (1998), Rijnders, Lanzendorf and the '607 patent are detailed above. They do not specifically teach that the feeder cells are passaged only 3 times, at most. However, Conner provide guidance to the preparation of mouse embryo fibroblast feeder cells, which are used to maintain human stem cells. See Thomson (2001), col. 8, lines 32-40; Thomson (1998), p. 1147, col. 2, #6. In particular, they suggest freezing the MEFs until use (p. 23.2.4, Freezing and Thawing MEFs). In particular, they teach the following:

> "The advantage of using MEFs is that they provide a more consistent source of feeder cells. Early passage cells with reproducible characteristics must be used because they rapidly lose their ability to divide. Long-term propagation of STO cells can lead to changes that result in characteristics that are less favorable for ES cell growth."
> See p. 23.2.6, Commentary, 2nd ¶, emphasis added.

Furthermore, Conner teach that MEFs are primary cells with limited mitotic potential, and that expanding the cells more may work, but the growth rate will decrease (see p. 23.2.7, 1st col., ¶2).

Accordingly, given the combined teachings, it would have been obvious to one of skill in the art, preparing human ES cells, and using embryonic fibroblasts as feeder cells, to use a early passage cell, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to use early passage embryonic fibroblasts, because Conner clearly teach that later passage cells lose the ability to divide, and can have changes in characteristics that are not conducive to ES cell growth. Although Conner do not specifically teach that the cells should be passaged less than 3 times, this would be well-within the knowledge of the skilled artisan that the less passages the embryonic fibroblasts are subjected to, the more conducive the feeder cells would be to maintain ES cells. Thus, using feeder cells that have been passaged less than 3 times would be well-within the skills of the ordinary artisan. Additionally, because Conner suggest that the MEFs should be frozen prior to use, this provides additional motivation and suggestion that the embryonic fibroblasts should not be subjected to many passages.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (2001) when taken with Thomson (1998) when taken Rijnders *et al.*, Lanzendorf *et al.* and in further view of US Pat. No. 6,875,607 (published April 5,

2005; filed November 9, 1999), as applied to claims 1-3, 5, 6, 12, 13, 16-20, 62, 64, 65 above, and in further view of Gardner *et al.* (1998), when taken with Gardner (1999).

Applicants provide no substantive arguments with respect to this rejection. The Examiner has addressed Applicants' arguments above.

Thomson (2001), Thomson (1998), Rijnders, Lanzendorf and the '607 patent are detailed above. They do not specifically teach culturing the blastocysts of step ii) or the inner cell mass of step iv) of claim in the presence of an agent, such as hyaluronic acid, to improve attachment of blastocysts. However, prior to the time of the claimed invention, Gardner teach that culturing of blastocysts in hyaluronic acid (hyaluronate) supports an increase in the implantation of blastocysts in IVF. See Abstract. Gardner teach that culturing human embryos in hyaluronate supports a significantly higher implantation rate (see page 155, 1st ¶); and that hyaluronate appears to be involved in the attachment of the blastocyst (see p. 155, 2nd ¶). Although Gardner's techniques are used in producing blastocysts that would be used in IVF, the fact that they show an improvement in attachment of the blastocyst is significant. They teach that studies in mice and cattle show that there is a relationship between the rate and normality of nutrient utilization and developmental potential, and that conventional embryo culture causes significant trauma in the developing embryo. Gardner (1999) provides teachings to show that, in mice, blastocyst cell numbers and overall development increased when embryos were cultured in hyaluronan. See Abstract.

Accordingly, in view of the combined teachings, it would have been obvious for one of skill in the art to modify the methods of Thomson (2001), Thomson (1998), Rijnders, Lanzendorf, and the '607 patent, by culturing either the blastocyst of step ii) or the ICM cells of step iv) in a culture medium that contained hyaluronic acid, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification, as Gardner and Gardner (1999)

provide guidance to show that culture medium that contains hyaluronic acid increases attachment of the blastocyst.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim 35 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (**U.S. Pat. No., 6,200,806 B1**, issued March 13, 2001, cited above) when taken with Stratagene Catalog, 1988, p. 39.

Applicants provide no substantive arguments with respect to this rejection. The Examiner has addressed Applicants' arguments above.

Accordingly, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Thomson into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control" (page 39, column 1).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632